REVIEW ARTICLE

Drug Safety 1999; Jan 20 (1): 43-57
0114-5916/99/0001-0043/$07.50/0

A Risk-Benefit Assessment of Abciximab in Angioplasty

Neal S. Kleiman

Baylor College of Medicine, The Methodist Hospital, Houston, Texas, USA

Contents

Abstract

Advances in percutaneous coronary intervention (PCI) have allowed procedures to be performed on a variety of patients with a spectrum of challenging coronary anatomy. Abciximab has permitted further expansion and has made the procedure safer. Abciximab is a chimerised murine monoclonal antibody directed against the platelet glycoprotein (GP) IIb-IIIa receptor. Binding to this receptor inhibits platelet aggregation to a wide variety of biological agonists. It also binds to $\alpha_v\beta_3$ and leucocyte MAC-1 receptors; the biological significance of its affinity to these receptors is unclear. Abciximab has an extremely short plasma half-life. Since abciximab binds to the platelet GP IIb-IIIa receptor with great avidity it has an extremely long biological half-life.

The use of abciximab is currently confined primarily to PCIs. The first large trial, EPIC, established that abciximab, given with aspirin (acetylsalicylic acid) and heparin, reduced the frequency of peri-procedural ischaemic events by 35% in high-risk patients. For this reduction a bolus of 0.25 mg/kg was followed by a

12-hour infusion of abciximab. However, the transfusion rate was doubled. A subsequent trial, EPILOG, indicated that reduction of the dose of heparin along with expeditious removal of arterial access sheaths, reduced the rate of haemorrhagic complications to a level comparable with placebo-treated patients, while also amplifying the reduction in ischaemic events.

In a third trial, EPISTENT, this benefit was shown to include patients undergoing elective coronary stent implantation. Additional trials have demonstrated that the same effect is present in patients undergoing primary PCI for acute myocardial infarction and in patients undergoing PCI for refractory unstable angina pectoris. In the latter situation, treatment with abciximab for 18 to 24 hours preceding the intervention reduced the rate of myocardial infarction even before the procedure was begun.

The rationale for the use abciximab is thus clearly established. Bleeding complications can be reduced by limiting the heparin dose, avoiding unneeded venous access site punctures, and expeditious removal of arterial sheaths. In emergency coronary artery bypass surgery, platelet transfusion reduces the number of receptors occupied per platelet and is likely to reduce the degree of postoperative bleeding.

The cost of abciximab remains an issue; however, this is partially offset by the reduction in ischaemic complications and accompanying resource use. In patients undergoing elective coronary stenting, abciximab use reduced the long term rate of target vessel revascularisation. The degree to which this reduction results in further cost savings will require further analysis.

1. What are the Clinical Needs?

Advances in percutaneous revascularisation techniques have led to a virtual explosion in the implementation of this technology. At the time of its initial development by Gruntzig et al.,[1] angioplasty was envisioned to be applicable to a small segment of the population with symptomatic coronary artery disease, specifically patients with single vessel involvement by a discrete concentric narrowing and stable angina of relatively new onset. However, angioplasty evolved rather rapidly and soon came to encompass a group of patients with a risk profile well outside that imaginable in the late 1970s, and early 1980s.

As the population undergoing percutaneous revascularisation has evolved to include those more seriously ill, and more patients with acute coronary syndromes undergo revascularisation, the potential consequences of ischaemic complications have increased. Even with modern technology, approximately 2% of patients undergoing coronary angioplasty sustain a Q wave myocardial infarction and as many as 10 to 20% release creatine kinase into the circulation, indicating myocardial necrosis.[2]

Although the significance of cardiac enzyme release after percutaneous intervention is still subject to some controversy, most databases which include long term follow-up indicate that this enzyme release is associated with a significant increase in late mortality[3] and sudden death in particular.[4] Abrupt vessel closure is also a phenomenon which occurs during intracoronary instrumentation and is associated with significant morbidity and economic expenditures.[5] Thus, despite significant advances in percutaneous revascularisation techniques and strategies, a need still exists for treatment strategies which will limit the adverse consequences of coronary angioplasty–related complications and improve the risk-benefit ratio of the procedure.

2. What is Abciximab?

Abciximab (c7E3 Fab) is the chimeric Fab fragment of a monoclonal antibody directed against the platelet glycoprotein IIb-IIIa (GP IIb-IIIa) receptor

complex. Platelet aggregation plays a central role in the early formation of arterial thrombosis.[6] The GP IIb-IIIa receptor complex is the most abundant protein on the platelet surface. It is a member of the integrin family and thus consists of 2 non-covalently linked subunits which exist in an inactive conformation on the resting platelet.

Following platelet activation, regardless of the stimulus, the GP IIb-IIIa receptor complex assumes an active conformation and permits platelet aggregation to occur through cross-linking with circulating multivalent macromolecular ligands, specifically fibrinogen and von Willebrand Factor.[7] This receptor complex may also play a role in the adhesion of platelets to immobilised fibrinogen on the injured endothelial surface.[8,9]

Approximately 80 000 such receptors are present on the surface of each platelet.[10] Abciximab attaches more rapidly to activated than unstimulated platelets, indicating that it preferentially recognises the activated form of the receptor,[11] and abolishes platelet aggregation and thrombosis in a dose-dependent fashion in response to a variety of platelet agonists. As such, it inhibits platelet aggregation considerably more effectively than aspirin or ticlopidine.[11,12] In *in vitro* experiments, binding of abciximab to platelets also reduced thrombin generation on the platelet surface,[13] possibly by inhibiting assembly of the prothrombinase and tenase complexes which require the presence of a phospholipid surface (in this case, the cell membrane of aggregated platelets) to catalyse the activation of prothrombin and factor X.[14]

Abciximab also binds to the integrins $\alpha_v\beta_3$[15] and MAC-1[16] although the biological significance of these interactions is uncertain. It is conceivable that the 2 binding affinities may be responsible for antiproliferative and anti-inflammatory properties, respectively, of abciximab.

3. Prevention of Thrombosis

The precise degree of receptor occupancy by abciximab required to inhibit platelet aggregation is not known. It is clear, however, that normal platelets contain excess GP IIb-IIIa receptors. In a Folts model of endothelial injury and stenosis, inhibition of cyclic flow variations (an indicator of intravascular platelet aggregation) abciximab manifests a dose-response effect while the more intense platelet stimulation associated with an electrolytic injury and reperfusion model requires that approximately 80% of surface receptors be occupied.[17] Similarly, *in vitro* models of thrombin generation on the platelet surface also suggest that a threshold is present.[13] On the other hand, indirect measurements of GP IIb-IIIa blockade with the peptide antagonist eptifibatide[18] suggest that in the IMPACT-II (Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II) study of eptifibatide during percutaneous coronary intervention (PCI),[19] prevention of abrupt closure during angioplasty[20] occurred when approximately 40 to 50% of receptors were occupied.

4. Pharmacokinetics and Pharmacodynamics

It is particularly important to understand the pharmacokinetics and pharmacodynamics of abciximab in order to understand tolerability and efficacy considerations. After administration, abciximab binds very rapidly and very avidly to circulating platelets and is quickly removed from the circulation,[21] probably through this mechanism. Since platelet aggregation returns to approximately 50% of its baseline value 6 hours after a bolus of abciximab is given and since the plasma half-life of abciximab is very short (approximately 10 minutes), it is necessary to follow a bolus injection with a continuous infusion to maintain steady state plasma concentrations. This strategy is able to sustain inhibition of platelet aggregation at the profound concentrations initially obtained with the bolus.[12] However, despite its very brief plasma half-life, abciximab remains avidly bound to platelet GP IIb-IIIa receptors for considerable periods of time. It therefore inhibits platelet aggregation for hours after it is administered and can still be found on the platelet surface at least 2 weeks after a bolus injection.[22,23]

Recovery of platelet function, then, occurs gradually rather than rapidly.[23] In this regard, the pharmacodynamic characteristics of abciximab differ greatly from the second generation of GP IIb-IIIa antagonists such as tirofiban, eptifibatide or lamifiban. These agents, which are characterised by less avid binding to the receptor complex, have higher plasma concentrations when the fluid and platelet-bound phases are in equilibrium. The result is that their plasma half-lives are longer than that of abciximab, but their duration of platelet inhibition is considerably shorter (in the presence of normal renal and hepatic function), since these molecules dissociate more readily from the receptor.

Despite high avidity of binding, the distribution of receptor occupancy by abciximab is monomodal,[23] indicating that abciximab molecules 'hop' between platelets. This feature plays an important role in patients who are referred for emergency bypass surgery, or who develop bleeding while receiving abciximab. Platelet transfusions introduce a new source of unoccupied GP IIb-IIIa receptor complexes. Since there is little to no extraplatelet reservoir of abciximab, the new platelets provide a 'sink' which reduces the percentage of receptors per platelet that are occupied. The result is that much of the haemostatic function of platelets is restored, and bleeding time returns toward normal.[24]

5. What is the Evidence that Abciximab is Beneficial?

5.1 Prevention of Acute Ischaemic Events During and After Percutaneous Coronary Intervention

Five large studies have been completed using abciximab in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). In the Evaluation of c7E3 Fab in the Prevention of Ischemic Complications trial (EPIC),[25] 2099 patients undergoing high risk (based on coronary angiography or the presence of an unstable ischaemic syndrome) coronary dilation were assigned to receive either standard treatment with aspirin (acetylsalicylic acid) and heparin or 1 of 2 abciximab regimens in addition to aspirin and heparin: an abciximab 0.25 mg/kg bolus alone, or a 0.25 mg/kg bolus followed by a 12 hour infusion at 10 μg/min. Patients assigned to the bolus and infusion had a highly significant 35% reduction in the composite of death, myocardial infarction or urgent revascularisation at 30 days, from 12.8 to 8.3% ($p = 0.008$).

In patients receiving the bolus alone, the reduction was not significant. Ischaemic events were suppressed shortly after the bolus was given, but began to occur approximately 6 hours later. In the bolus alone group, the rate of ischaemic events ultimately approached that of the placebo group, while in the bolus/infusion group, events were suppressed for the duration of the infusion and the slight increase in events at the termination of the infusion did not catch up to those in the placebo group. However, these benefits were achieved at the cost of a significant increase in the rate of bleeding, from a 7% transfusion rate in the placebo group to 15% in the bolus/infusion group.[25]

Three-quarters of the major bleeding events occurred at the site of arterial puncture. Interestingly, the risk of major bleeding was associated with the initial bolus dose of abciximab, and was not substantially increased by continuation of the infusion.[26] Subsequent analysis of this database identified several key determinants of bleeding; including age, female gender, low bodyweight, and procedural heparin dose. In addition, the protocol for this study required that arterial access sheaths be left in place for 18 to 24 hours and that patients receive continuous intravenous heparin during this time.[26]

As a consequence of these findings, a second study of abciximab EPILOG (Evaluation of PTCA to Improve Long-term Outcome by cF7E3 Glycoprotein Receptor Blockade),[27] was performed to evaluate the role of heparin in preventing thrombosis and to determine its contribution to bleeding in patients treated with abciximab. In this trial, all patients, regardless of perceived risk, were eligible for enrolment. Patients were randomised to receive either standard therapy with aspirin and heparin

with the activated clotting time adjusted to >300 seconds, or abciximab 0.25 mg/kg bolus followed by 0.125 μg/kg/min infusion for 12 hours with 1 of 2 heparin regimens: standard weight-adjusted heparin therapy (100 U/kg bolus with activated clotting time adjusted >300 seconds) or low dose weight-adjusted heparin therapy (70 U/kg without activated clotting time adjustment and subsequent hourly boluses of supplemental heparin).

Although the latter dose of heparin may seem low for patients undergoing PCI, abciximab raises the activated clotting time beyond the level seen in patients receiving comparable doses of heparin without abciximab[27] and the median activated clotting time in the low dose heparin group was 228 seconds. The mechanism of this interaction is not completely explained, but may be related to the GP IIb-IIIa antagonist interfering with assembly of a phospholipid surface sufficiently large to permit assembly of either the prothrombinase or tenase complexes.

In EPILOG as in EPIC, the composite of death, myocardial infarction, or urgent revascularisation within the first month after the procedure was reduced significantly by abciximab. However, the reduction was greater than that seen in EPIC and was actually greatest in patients assigned to receive abciximab with low dose heparin. Arterial access sheaths could be removed several hours after the procedure and the result was that transfusion rates were low in all 3 treatment groups, and in the group receiving abciximab with low dose heparin these rates were lower than in the placebo group.[28]

A third study also provides evidence of the efficacy of abciximab in PCI. In CAPTURE (C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina),[29] 1265 patients with refractory unstable angina who were scheduled for angioplasty were assigned to receive either abciximab or placebo, administered for 18 to 24 hours before PCI and for 1 hour afterward. In this study, the composite risk of death, myocardial infarction or urgent revascularisation was reduced from 15.9 to 11.3% at 30 days in the abciximab group. By 6 months, however, attrition of this result had occurred and there were no differences between the abciximab or placebo groups in the composite end-point of death, myocardial infarction or repeat revascularisation. However, a 50% reduction was observed in the composite of death or myocardial infarction in the abciximab group and this remained robust throughout the 6-month period. In fact, the reduction in myocardial infarction began even during the period before the angioplasty was begun. This benefit was especially pronounced in patients with elevations in serum troponin T.[29]

A fourth recently completed study, RAPPORT (ReoPro in Acute Myocardial Infarction and Primary PTCA Organisation and Randomised Trial),[30] provides further evidence for the use of abciximab in unstable syndromes. In this study, patients undergoing primary PTCA for acute myocardial infarction who had ST segment elevation were randomised to receive either abciximab or standard therapy, consisting of aspirin and heparin. Patients receiving abciximab had a 46% reduction in the risk of death or recurrent infarction by the time of hospital discharge, and the need for salvage ('bail-out') stent placement was similarly reduced.[30]

Finally, a fifth study, EPISTENT (Evaluation of IIb/IIIa Platelet Inhibitor for Stenting),[31] involved 2399 patients randomised to placement of a Palmaz-Schatz stent alone, stent placement accompanied by abciximab (0.25 mg/kg bolus and 12-hour infusion at 0.125 μg/kg/min) or to PCI with abciximab and no stent placement. Abciximab reduced the composite of death, myocardial infarction, or urgent revascularisation from 10.8% in the stent alone group, to 5.3% in the stent with abciximab and 6.9% in patients receiving PCI with abciximab but without a stent.[31] This reduction consisted largely of the prevention of the composite of death or large (CK >5x) control myocardial infarction. After 6 months, the difference favouring abciximab combined with stenting was still maintained.

5.2 Target Vessel Revascularisation

A prominent feature of the EPIC trial was the reduction in the secondary end-point of death,

myocardial infarction, or revascularisation at 6 months. Further analysis of these data revealed that revascularisation of the target vessel was reduced by 26% at 6 months.[32] The EPIC trial investigators interpreted these findings as indicative of a reduction in clinical restenosis. Various theoretical mechanisms have been invoked to explain these findings, particularly reduced platelet-induced stimulation of extracellular matrix deposition[33] and abciximab antagonism of the $\alpha_v\beta_3$-receptor (vitronectin receptor).[34,35] The latter receptor is expressed on a variety of cells including platelets and smooth muscle cells and is believed to play an important regulatory role in the cellular proliferation phase of restenosis.[36] Abciximab binds $\alpha_v\beta_3$ with avidity equal to that of GP IIb-IIIa, and is probably exchanged between receptors.[15]

Unfortunately, subsequent trials failed to confirm this benefit of abciximab clearly. In neither the EPILOG, RAPPORT, nor CAPTURE trials was a reduction observed in the rates of target vessel revascularisation at 6 months. A smaller study, ERASER, studied the effects of abciximab, given as a bolus followed by 12- or 24-hour long intravenous infusions, on restenosis assessed by intracoronary ultrasound, and also failed to provide evidence of a reduction in restenosis.[37]

The 6-month results of EPISTENT provided more data on the effect of abciximab on cellular proliferation. Between the second and third months after the angioplasty, rates of target vessel revascularisation in the abciximab-alone group equilibrated with those in the 2 stented groups. Therefore, at 6 months, target vessel revascularisation rates were higher in patients receiving abciximab alone, compared with those receiving stents. Interestingly, the rate of target vessel revascularisation was lowest in patients assigned to combined abciximab and stent placement compared with the group assigned to stenting alone. The differences were most pronounced in patients with diabetes mellitus.[38] These clinical findings were supported by the results of an angiographic substudy of EPISTENT. Since stent placement minimises arterial recoil and remodelling components of restinosis, these findings raise the possibility that abciximab exerts an antiprofliferative effect, possibly through its binding to $\alpha_v\beta_3$.

6. What are the Risks Associated with Abciximab?

The primary risk associated with abciximab is bleeding. In EPIC,[25] the risk of transfusion was doubled in the abciximab-treated group compared with placebo. Nearly 3 out of 4 haemorrhages that occurred in this study were at the site of femoral arterial access, but there were also a substantial number of gastrointestinal haemorrhages. It is likely that several factors were operative in elevating the bleeding rates, including exuberant use of heparin during the era in which the study was done, relatively long periods during which access sheaths were left in place, and the lack of a codified transfusion policy during the study.

Subsequent analysis,[26] and a pilot study (Precursor to EPILOG, PROLOG),[39] suggested that the risk of haemorrhage could be lowered significantly by a reduction in the amount of heparin given during and after the procedure as well as by early removal of the femoral arterial sheath as soon as the heparin had been metabolised.[39] As mentioned in section 5.1, reduction in the dose of heparin in EPILOG coupled with rapid sheath removal and reduction of the abciximab infusion to 0.125 μg/kg/min reduced the rate of major bleeding to a level comparable to that of the placebo group although there was still an excess of minor bleeding.[28] In CAPTURE,[29] the rate of haemorrhage was substantially higher than that seen in EPILOG, and may have been due to both higher heparin dose administration in the former study as well as to the fact that patients in CAPTURE were fully anticoagulated and had ongoing abciximab and heparin therapy at the time femoral puncture for arterial access was performed. Thus, although the rate of haemorrhage is in general low, patients who already have received heparin, either in the form of a continuous infusion, or as part of an angioplasty procedure that has already begun, appear to be at increased risk of bleeding.

Very few episodes of abciximab-related bleeding are truly life threatening. In none of the trials of abciximab or, in fact of any of the other GP IIb-IIIa antagonists, has there been an excess of intracranial haemorrhage. It becomes important then, to recognise which patients are at greatest risk for bleeding complications. In EPIC, several baseline clinical characteristics were predictive of an increased risk of major haemorrhage. In particular, the risk was increased nearly 4-fold in patients within the first 12 hours of an acute myocardial infarction, was higher in patients with low bodyweights, and increased as the age of the patient increased. Each additional 10 years of age increased the risk of major haemorrhage 1.25-fold.

Other procedural variables such as insertion of an intra-aortic balloon pump, duration of the procedure, and increasing heparin dose were also major factors in predicting haemorrhage. Based on these factors, a regression model was developed to predict a 'blood loss index'.[26] However, changes in modern practice, including the use of lower doses of heparin during PCI with abciximab, the use of smaller arterial access sheaths, less frequent placement of venous sheaths, and the earlier decision to place intracoronary stents have reduced the risk of haemorrhage considerably.

On the other hand, the advent of newer technologies has also changed the spectrum of patients undergoing PCI. Patients with renal insufficiency and patients with recent strokes were not eligible for the early trials of abciximab, and data are now only beginning to be accumulated in these patient groups. Among patients with mild to moderate degrees of renal insufficiency, accumulated data do not indicate a relationship between creatinine clearance and bleeding risk, but it must be remembered that patients with severe renal insufficiency often have significant comorbidity in addition to a defect in platelet function, and the range of creatinine clearances studied has been limited.

The other significant risk associated with abciximab is thrombocytopenia. The mechanism of this complication is not known. Thrombocytopenia, defined as platelet count less than 20 000/mm^3 occurred in 1% of patients enrolled in EPIC.[25,40] Placebo-controlled studies thus far have been confined to first administration of abciximab, but preliminary observations suggested that prior exposure to abciximab may increase the rate of thrombocytopenia,[41] although a more formal assessment indicates that this excess may be less profound than previously thought.[42]

7. Who Benefits Most from Abciximab?

Abciximab is currently indicated for the prevention of ischaemic events as a consequence of high risk angioplasty. The finding from the EPILOG trial that the reduction in risk was distributed across all patient groups recently led the US Food and Drug Administration to expand the indication for abciximab to include all patients undergoing PCI.

If cost were not an issue, then the data would argue irrefutably that abciximab should be given to all patients undergoing PCI. Previous studies have encompassed patients with a broad spectrum of risks, from patients with evolving myocardial infarction in RAPPORT, through to those with refractory unstable angina in CAPTURE, to the (relatively) lower risk groups in EPIC, EPILOG and EPISTENT.

In each of these trials, there has been benefit across the entire spectrum of perceived risk. In fact, data from the IMPACT-II study of eptifibatide suggest that PCI operators are relatively poor at distinguishing patients at high risk from those at low risk.[19]

However, abciximab is relatively expensive [approximately $US1500 (1998 value) for the average sized patient]. In EPIC,[25] treatment with abciximab led to a savings of approximately $US1270 (1992 value) per patient. Hospital costs were increased, largely as a result of the excess in bleeding complications. However, the total cost of care at the end of 6 months was reduced as a result of a reduction in revascularisation procedures.[43]

In contrast, data from EPILOG did not support a reduction in revascularisation procedures at 6 months, and even despite the reduction of death or

myocardial infarction, the total cost of care was $US780 (1994 value) greater in patients treated with abciximab.[44] The lower rate of bleeding halved the cost of in-hospital care.[44] It is therefore still important to identify patient groups in whom the benefit is likely to be greatest. The most obvious source of such information, of course, lies in the various subgroups of patients studied in the placebo-controlled trials of abciximab. However, it must be kept in mind that subgroup analysis, by definition, involves small numbers of patients in whom statistical power to reach meaningful and definitive conclusions is almost never present. Thus, selection of patients for treatment with abciximab will rely nearly as much on pathophysiological considerations and background information as on data from subgroups within the large clinical trials.

7.1 Atherectomy

Coronary atherectomy exposes relatively large areas of the arterial lining to blood flow, perhaps larger areas with deeper injury, than those exposed by balloon angioplasty. While the residual lumen is larger than that remaining after PCI,[45] the resulting milieu is more likely to be favourable to thrombosis.

Evidence from CAVEAT (Coronary Angioplasty Versus Excisional Atherectomy Trial)[45] indicates that indeed, the rate of non–Q wave myocardial infarction is higher following directional coronary atherectomy than following PCI,[46] and that patients in whom creatine kinase elevations occur are at increased risk for subsequent cardiac events.[47]

Similarly, the Balloon vs Optimal Atherectomy Trial (BOAT)[48] investigators demonstrated a higher risk of creatine kinase elevation following directional atherectomy than balloon angioplasty. However, the risk of mortality during the first year associated with creatine kinase elevation after successful revascularisation in this trial was not higher than that observed in the absence of creatine kinase release, perhaps due to a lower risk patient population and shorter follow-up in this trial.[48]

Both EPIC[25] and EPILOG[28] confirmed that twice as many patients undergoing directional atherectomy develop non–Q wave infarction, (defined by creatine kinase rise to more than 3 times the upper limit of normal) compared with patients undergoing angioplasty. In both studies, treatment with abciximab halved the rate of non–Q wave infarction among patients undergoing directional atherectomy, thus reducing the risk of infarction to that comparable with PCI alone.[49,50]

Use of abciximab in these patients, therefore, appeared favourable, but should be balanced against the higher risk of femoral arterial bleeding associated with the larger sheath size and more traumatic guiding catheters required for directional coronary atherectomy. (Although the rates of peri-access site bleeding in EPIC were similar for both angioplasty and directional atherectomy groups, the sample size and event rates do not exclude a higher bleeding rate in patients requiring larger sheath sizes.)

Patients undergoing rotational atherectomy were excluded from both EPIC[25] and EPILOG;[28] however, rotational atherectomy is often complicated by particulate sludge in the distal coronary bed, the so-called ‘no-reflow’ phenomenon, and it has also been suggested but not confirmed that the rate of non–Q wave infarction is also slightly higher in patients undergoing rotational atherectomy, either as a result of deep tissue exposure or due to embolisation of microparticles.[51] In addition, high speed rotation of the burr may activate platelets through mechanisms related to mechanical shear.[52] No randomised study has demonstrated efficacy of abciximab in this setting; however, a number of registries have suggested that abciximab may lower the rate of creatine kinase release following rotational atherectomy.[53,54]

7.2 Diabetes Mellitus

The effect of abciximab in the patients with diabetes mellitus has been the subject of a good deal of misunderstanding recently. While the rate of periprocedural complications among people with diabetes was formerly higher than in those without

diabetes, more recent studies have indicated that with current angioplasty techniques, the complication rates are comparable.[55] However, in the recent National Heart, Lung and Blood Institutes (NHLBI)–sponsored Bypass Angioplasty Revascularisation Investigation (BARI) trial, mortality rates 5 years after angioplasty were almost twice as great among people with diabetes as among those without diabetes.[55] Since the short term event rates were comparable, these differences appeared to be the consequence of the greater extent of atherosclerotic disease in patients with diabetes. Restenosis rates have also been reported to be higher in individuals with diabetes than in those without diabetes,[56] although a recent report indicates that intracoronary stenting may reduce this differential.[57]

There are also differences between the coagulation systems of people with diabetes and people without diabetes. Platelets are likely to be larger, have more surface GP IIb-IIIa receptors per platelet, and to express P selectin on their surface, indicating platelet activation.[47,58,59] Thus, there is reason to believe that people with diabetes would benefit especially from treatment with a GP IIb-IIIa antagonist during angioplasty.

In EPIC,[25] abciximab had similar effects in both individuals with diabetes and those without diabetes. In EPILOG,[28] however, the reduction in death or myocardial infarction was greater in individuals with diabetes than those without diabetes, both at 30 days and at 6 months. In contrast to what was seen in people without diabetes, people with diabetes receiving abciximab in combination with standard dose heparin therapy had lower rates of death or myocardial infarction than people with diabetes who received abciximab in addition to low dose weight adjusted heparin.[60] In EPIST-ENT,[31] there was also a greater reduction in long term events in patients with diabetes mellitus than those without.

7.3 Acute Ischaemic Coronary Syndromes

A small number of patients in EPIC[25] underwent PCI for evolving myocardial infarction, either as primary therapy for the infarction (primary PCI) or as rescue therapy within 24 hours of failed thrombolysis. In this group, the combination of a bolus followed by continuous infusion of abciximab led to a reduction in the rate of death, myocardial infarction, or urgent revascularisation from 56 to 5% at 6 months.[61]

This difference is perhaps somewhat greater than what would usually be expected in a larger patient population, but has been nonetheless confirmed by the recent findings of the RAPPORT trial. In this trial of 440 patients, the composite of death or myocardial infarction was reduced from 11.2 to 8.7% at 6 months using an intention to treat analysis and 12 to 6.9% using an analysis of all treated patients.[30]

Another qualitatively similar group was composed of patients with unstable angina or non–Q wave myocardial infarction, particularly those with dynamic ST-segment shifts. In EPIC, among patients with unstable angina, the composite endpoint of death, myocardial infarction, or urgent revascularisation by 30 days was reduced 62% among patients with unstable angina compared with 27% among patients with stable angina. This difference became increasingly wide as time progressed and at 3 years there was a significant reduction in mortality among patients who underwent PCI for unstable angina or evolving myocardial infarction.[34]

That treatment with abciximab should be most striking in these groups is concordant with current concepts about the pathophysiology of acute coronary syndromes. Pathological findings indicate that the majority of acute coronary syndromes result from disruption of an atherosclerotic plaque and the subsequent activation of both platelets and the soluble coagulation cascade as a result of changes at the plaque surface. Since mechanical intervention results in deep fissures in the target atherosclerotic plaque and the surrounding vessel, the likelihood of intravascular thrombosis is further increased in the setting of a prothrombotic milieu.

Interestingly, patients in whom intracoronary thrombi can be identified based on angiograms performed before the procedure, do not seem to have any added benefit compared with those in whom intravascular thrombi cannot be visualised,[62] suggesting that the clinical setting for abciximab therapy may be more important than the angiographic findings.

8. How Should Abciximab be Given?

In each of the studies which showed a benefit, abciximab was administered prior to beginning the PCI procedure. Although it is a very common practice to administer abciximab after the outcome of an angioplasty appears to be suboptimal, 3 important caveats should be noted. First, there are few data – either clinical or pharmacodynamic – supporting the use of abciximab in this setting. An observational study suggests that abciximab aids the resolution of a thrombus which forms within a coronary artery during PCI procedures;[63] however, randomised studies demonstrating clinical efficacy of 'rescue' abciximab have not been performed. Second, platelet activation and deposition begin almost immediately following balloon injury,[64] and may not be reversed by treatment with abciximab. It is also conceivable that platelets stimulated intensely by balloon injury to the vessel may be in a more activated state, express more GP IIb-IIIa receptors, and therefore may not be inhibited adequately by the standard dose of abciximab. Finally, angioplasty is usually performed with doses of heparin which are higher than those normally given with abciximab, and the operator is thus left with the choice of accepting a potentially higher risk of bleeding or with reversing (either completely or partially) the heparin with protamine.[65]

Another approach that is increasing in popularity is to begin therapy with abciximab in patients with acute ischaemic syndromes prior to arrival in the cardiac catheterisation laboratory. This practice is based upon the results of the CAPTURE trial.[29] The use of abciximab in this manner, that is upon presentation with an acute coronary syndrome rather than waiting for PCI, is appealing and is in fact supported by a number of trials of peptide and peptidomimetic GP IIb-IIIa antagonists in the setting of acute ischaemic syndromes.[66-68]

9. What are the Alternatives to Abciximab?

Until recently, abciximab was the only GP IIb-IIIa antagonist available commercially. The peptide eptifibatide and the nonpeptide tirofiban have become available within the past few months. Although all patients undergoing PCI receive treatment with aspirin, other antiplatelet therapy is not available, and there is only marginal evidence supporting an advantage for treatment with ticlopidine (in the absence of stent placement).

In the minds of many angioplasty operators, intracoronary stenting represents an alternative to abciximab therapy. This mindset is particularly appealing both on economic grounds, since the cost of either therapy is significant, and on certain theoretical grounds. Stent placement is able to seal large intimal flaps against the arterial wall and to eliminate vascular recoil, thus assuring the successful restoration of a large intravascular lumen with no impingement to the smooth flow of blood. It is likely that vigorous antegrade blood flow is able to wash platelet aggregates off the lumenal wall. Data supporting the use of stents to reduce restenosis are also compelling, while those for an antirestenotic effect of abciximab therapy (in the absence of stents) derive predominantly from a single study.

From a practical point of view, the issue is less clear. A recent study (EPISTENT) in which stent placement with and without abciximab therapy were compared with angioplasty with abciximab but without a stent has recently been completed (see section 5.1). Data from this study suggest that abciximab reduces target vessel revascularisation in stented patients. Several points should be kept in mind, however. First, coronary angioplasty is a part of every stent procedure, and many of the thrombotic complications of PCI, including side branch occlusion, distal embolisation, and transient abrupt closure can accompany either proce-

dure. It is also uncommon for the entire endothelial surface which is disrupted to be covered by the stent. Coverage of the entire dilated region may not be desirable since longer stented areas may also be associated with higher rates of restenosis.[69] It is therefore conceivable that, from a procedural point of view, abciximab will increase the safety of stent placement and thus allow the angioplasty operator to place fewer stents or to cover shorter areas of the target lesion with a stent in the future, even shorter areas of dilated vessel may be covered with a stent.

Second, although current stent placement techniques have made subacute stent thrombosis quite uncommon in general, rates of stent closure are still high in small vessels or those requiring multiple stents.

Finally, it should be borne in mind that in none of the trials in which stent placement was shown to be superior to angioplasty without stent deployment, was stenting shown to be associated with a reduction in the rate of either myocardial infarction or death. In fact, evidence of creatine kinase release was present in 20% of patients undergoing stent placement in a recent large randomised trial.[2]

Thus, although there is likely to be some overlap between the ability of either therapy to prevent occlusion of major arterial trunks, it also likely that there are many cases in which combined therapy is also indicated. In support of this contention, it should be noted that in each of the major trials of GP IIb-IIIa antagonists, the rate of death or myocardial infarction was reduced significantly in patients receiving 'bail-out' stents and the GP IIb-IIIa antagonist compared with patients receiving bail-out stents with the placebo treated group.

10. Other Issues

10.1 Ticlopidine

The increased frequency of stent placement has led many practitioners to treat patients with ticlopidine beginning several days prior to a planned PCI, in anticipation of stent placement. Ticlopidine is a weak platelet antagonist which affects primarily adenosine diphosphate (ADP)–induced platelet aggregation through an uncertain mechanism. This effect is not evident until several days after therapy is begun. *Ex vivo* experiments in patients treated with ticlopidine indicate that after 24 hours of therapy only minimal changes in the concentration of abciximab necessary to reduce platelet aggregation by 50% (IC_{50}) of abciximab can be detected, but after 7 days of treatment, the IC_{50} of abciximab is reduced by approximately 30%.[70]

When ticlopidine is given the night before therapy with abciximab, peak inhibition of platelet aggregation by abciximab is not affected, but as expected, the rate at which platelet aggregation recovers after termination of abciximab therapy is delayed. When ticlopidine is begun 3 days prior to abciximab therapy, peak inhibition of platelet aggregation is increased, and the recovery phase is prolonged even further.[71] The safety of combining these 2 antiplatelet therapies (with aspirin as well) is not known although data from the EPIST-ENT trial do not suggest an increased rate of haemorrhage.[31]

10.2 Oral Glycoprotein IIb-IIIa Antagonists

As oral antagonists of the GP IIb-IIIa complex are introduced, the safety of combining these agents with abciximab is likely to become a clinical issue. In many high risk patients, particularly those with less than satisfactory results of PCI, it is appealing to prolong the period of GP IIb-IIIa inhibition until re-endothelialisation of the disrupted arterial wall can occur. Binding of abciximab to the GP IIb-IIIa receptor complex involves a site distinct from that occupied by compounds mimicking the arginine-glycine-asparagine (R-G-D) sequencing necessary for the recognition of fibrinogen and von Willibrand factor by the GP IIb-IIa receptor. The effects of abciximab and these compounds may therefore not be completely additive, although there is likely to be some compounding of antiplatelet effect.

Kereiakes et al.[72] reported 17 patients who were treated with the oral GP IIb-IIIa antagonist

xemilofiban beginning 8 to 18 hours after completing an infusion of abciximab. The initial degree of platelet inhibition was greater than that seen in patients who received the same doses of xemilofiban without antecedent abciximab, but after one week of treatment there were no longer any differences between patients who did or did not receive abciximab.

In a larger study of xemilofiban given immediately after PCI, approximately one-third of patients received abciximab during the index procedure. These patients were treated with xemilofiban 10mg 3 times daily for 2 weeks while patients who did not receive abciximab during angioplasty were treated with xemilofiban 20mg 3 times daily. No excess bleeding was observed among the patients receiving abciximab followed by reduced dose abciximab.[73]

From these preliminary data, it seems that oral GP IIb-IIIa antagonists will be able to be administered safely to patients who have received abciximab, although a delay of several hours following the infusion would seem prudent, as would reduction in the initial dose for the first several days.

10.3 Emergency Surgery

Fortunately, in the era of salvage or 'bail-out' stenting, fewer than 1% of patients undergoing PCI require emergency bypass surgery. Nonetheless, this possibility still exists and may be even more likely in the high risk group of patients who are candidates for treatment with abciximab. For obvious reasons, the presence of a high degree of inhibition of platelet aggregation during coronary artery bypass surgery is not desirable.

Data on a small number of patients who underwent emergency bypass surgery in the EPIC study are available. Boehrer et al.[74] reported that the high rates of transfusion and life-threatening haemorrhage were no different between abciximab- and placebo-treated patients. However, it is important to remember that this comparison is between 2 groups of high risk patients undergoing emergency rather than elective coronary artery bypass.

Several points should be kept in mind. First, the threshold for sending a patient to emergency bypass may be different in a patient who receiving abciximab than in one who has not. In the presence of a residual dissection, abciximab may protect against abrupt closure or myocardial infarction,[75] thus making the need for emergency bypass less likely, or at least less pressing. When possible, delaying the onset of surgery will allow recovery of platelet aggregation to levels which are likely to be better tolerated during surgery.

Gammie et al.[76] reported on 11 patients undergoing emergent surgery and noted that when surgery was performed more than 12 hours after stopping abciximab, chest tube drainage and transfusion requirements were dramatically lower than when surgery was performed as an emergency. When emergency surgery is needed, however, it is recommended that lower doses of heparin be used when initiating cardiopulmonary bypass and that heparin be titrated to the activated clotting time.

In patients going to emergency bypass surgery, the abciximab infusion should be stopped and between 10 and 30 units of platelets should be given. The timing of the transfusion is controversial. In many centres, platelet transfusions are given before surgery is actually begun. On the other hand, cardiopulmonary bypass induces a haemostatic defect of its own.[77] Blockade of the GP IIb-IIIa receptor has even been suggested as a way to reduce platelet consumption while patients are supported by the bypass circuit. Therefore, many surgeons prefer that platelet transfusions be given after the patient is weaned from cardiopulmonary bypass.

11. Conclusions

The risk-benefit profile of abciximab has been reviewed. Overall, each placebo-controlled trial of abciximab in PCI has demonstrated a clinically meaningful reduction in the risk of death, myocardial infarction, and urgent revascularisation, with the longest follow-up also demonstrating a reduction in mortality alone in the highest risk patients. A reduction in clinical restenosis has not been demonstrated. While the earliest study, EPIC, also

showed an increase in the risk of bleeding associated with abciximab, the rates of haemorrhage have fallen in each subsequent study. Factors likely responsible for this decrease include reduction in the dose of heparin used, earlier removal of arterial sheaths, avoiding placement of femoral venous access sheaths, and weight adjustment of the abciximab infusion. It is likely, that as clinical practice evolves, several trends will add to this reduction even further, including a continued trend to avoid intravenous heparin infusions after angioplasty, use of smaller sheath sizes, and more frequent PCI using the transradial approach.

Economic issues are still important considerations in deciding whether to use abciximab. Although the spectrum of patients benefited has now been shown to include patients with evolving myocardial infarction, patients with unstable angina, those with stable angina, and those undergoing stent placement and atherectomy, the decision to use abciximab will most likely need to be individualised based on the risk that is felt to accrue from infarction in the distribution of a particular vessel.

References

1. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979; 301: 61-8
2. Leon, MB, Baim DS, Gordon P, et al. Clinical and angiographic results from the Stent Anticoagulation Regimen Study (STARS) [abstract]. Circulation 1998; 94 Suppl. I: I-165
3. Abdelmeguid AE, Topol EJ, Whitlow PL, et al. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. Circulation 1996; 94: 1528-36
4. Kong TQ, Davidson CJ, Meyers SN, et al. Prognostic implication of creatine kinase elevation following elective coronary artery interventions JAMA 1997; 277: 461-6
5. Detre KM, Holmes DR Jr, Holubkov R, et al.Incidence and consequences of periprocedural occlusion: the 1985-1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1990; 82: 739-50
6. Friedman M, Van den Bovenkamp GJ. The pathogenesis of a coronary thrombus. Am J Pathol 1966; 48: 19-44
7. Plow EF, McEver RP, Coller BS, et al. Related binding mechanisms for fibrinogen, fibronectin, von Willebrand factor, and thrombospondin on thrombin-stimulated human platelets. Blood 1985; 66: 724-7
8. Weiss HJ, Turitto VT, Baumgartner HR. Further evidence that glycoprotein IIb-IIIa mediates platelet spreading on subendothelium. Thromb Haemost 1991; 65: 202-5
9. Weiss HJ, Hawiger J, Ruggeri ZM, et al. Fibrinogen-independent platelet adhesion and thrombus formation on subendothelium mediated by glycoprotein IIb-IIIa complex at high shear rate. J Clin Invest 1989; 83: 288-97
10. Wagner CL, Mascelli MA, Neblock DS, et al. Analysis of GPIIb/IIIa receptor number by quantification of 7E3 binding to human platelets. Blood 1996; 88: 907-14
11. Coller BS. A new murine monoclonal antibody reports an activation-dependent change in the conformation and/or microenvironment of the platelet glycoprotein IIb/IIIa complex. J Clin Invest 1985; 76: 101-8
12. Tcheng JE, Ellis SG, George BS, et al. Pharmacodynamics of chimeric glycoprotein IIb/IIIa integrin antiplatelet antibody Fab 7E3 in high-risk coronary angioplasty. Circulation 1994; 90: 1757-64
13. Reverter JC, Beguin S, Kessels H, et al. Inhibition of platelet-mediated, tissue factor-induced thrombin generation by the mouse/human chimeric 7E3 antibody. J Clin Invest 1996; 98: 863-74
14. Krishnaswamy S, Jones KC, Mann KG. Prothrombinase complex assembly: kinetic mechanism of enzyme assembly on phospholipid vesicles. J Biol Chem 1988; 263: 3823-34
15. Tam SH, Jordan RE, Nakada MT. Abciximab (ReoPro, chimeric 7E3 Fab) demonstrates equivalent affinity and functional blockade of glycoprotein IIB/IIIA and $\alpha_v\beta_3$ integrins. Circulation 1998; 98: 1085-91
16. Simon DI, Xu H, Ortlepp, et al. 7E3 monoclonal antibody directed against the platelet glycoprotein IIb/IIIa cross reacts with the leucocyte integrin Mac-1 and blocks adhesion to fibrinogen and ICAM-1. Arterioscler Thromb Vasc Biol 1997; 17: 528-35
17. Gold HK, Coller BS, Yasuda T, et al. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet GPIIb/IIIa antibody in a canine preparation. Circulation 1988; 77: 670-7
18. Phillips DR, Teng W, Arfsten A, et al. Effect of Ca2+ on GP IIb-IIIa interactions with integrilin: enhanced GP IIb-IIIa binding and inhibition of platelet aggregation by reductions in the concentration of ionized calcium in plasma anticoagulated with citrate. Circulation 1997; 96: 1488-94
19. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention – IMPACT-II. Lancet 1997; 349: 1422-8
20. Blankenship JC, Sigmon KN, Tardiff BE, et al. Effect of glycoprotein iib/iiia receptor inhibition on specific in-lab complications of coronary intervention and resultant CKMB elevation in the IMPACT II trial [abstract]. Circulation 1996; 94: I-198
21. Kleiman NS, Raizner AE, Jordan R, et al. Differential inhibition of platelet aggregation induced by adenosine diphosphate or a thrombin receptor-activating peptide in patients treated with bolus chimeric 7E3 Fab: implications for inhibition of the internal pool of GPIIb/IIIa receptors. J Am Coll Cardiol 1995; 26: 1665-71
22. Konstantopoulos K, Kamat SG, Schafer AI, et al. Shear-induced platelet aggregation is inhibited by *in vivo* infusion of an anti-glycoprotein IIb/IIIa antibody fragment, c7E3 Fab, in patients undergoing coronary angioplasty. Circulation 1995; 91: 1427-31
23. Mascelli MA, Lance ET, Wagner CL, et al. Abciximab [7E3] pharmacodynamics demonstrate an extended and gradual recovery from GP Ib/IIIa blockade [abstract]. Circulation 1996; 96: I-513

24. Kereiakes DJ. Prophylactic platelet transfusion in abciximab-treated patients requiring emergency coronary bypass surgery [abstract]. Am J Cardiol 1998; 81: 373
25. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-61
26. Aguirre FV, Topol EJ, Ferguson JJ, et al. Bleeding complications with the chimeric antibody to platelet glycoprotein IIb/IIIa integrin in patients undergoing percutaneous coronary intervention. Circulation 1995; 91: 2882-90
27. Moliterno DJ, Califf RM, Aguirre FV, et al. Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (the EPIC trial): Evaluation of c7E3 Fab in the Prevention of Ischemic Complications trial. Am J Cardiol 1995; 75: 559-62
28. The EPILOG Investigators. Platelet glycoprotein IIB/IIIA receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997; 336: 1689-96
29. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina – the CAPTURE Study. Lancet 1997; 349: 1429-35
30. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randominsed Trial (RAPPORT) Investigators. Circulation 1998; 98: 734-41
31. The EPISTENTStudy Group. Randomised placebo-controlled and balloon angioplasty controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIB/IIIA blockade. Lancet 1998; 352: 87-92
32. Topol EJ, Califf RM, Weisman HF, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. Lancet 1994; 343: 1434-5
33. Schwartz RS, Holmes DRJ, Topol EJ. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. J Am Coll Cardiol 1992; 20: 1284-93
34. Topol EJ, Ferguson JJ, Weisman HF, et al. on behalf of the EPIC Investigator Group. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. JAMA 1997; 278: 479-84
35. Le Breton H, Rabbani R, Moussa S, et al. The role of integrins $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) and $\alpha_v\beta_3$ (the vitronectin receptor) in a guinea pig model of restenosis [abstract]. Circulation 1997; 94: I-517
36. Stromblad S, Cheresh DA. Cell adhesion and angiogenesis. Trends Cell Biol 1996; 6: 462-8
37. Ellis SG, Serruys, Popma JJ, et al. Can abciximab prevent neointimal proliferation in Palmaz-Schatz stents? The final ERASER results [abstract]. Circulation 1997; 96 Suppl.: 87
38. Husten L. Regimen lowers rate of coronary events in diabetes. Lancet 1998; 352: 711
39. Lincoff AM, Tcheng JE, Califf RM, et al. on behalf of the PRO-LOG Investigators. Standard versus low-dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 Fab) during percutaneous coronary revascularization. Am J Cardiol 1997; 79: 286-91
40. Berkowitz SD, Harrington RA, Rund MM, et al. Acute profound thrombocytopenia after C7E3 fab (abciximab) therapy. Circulation 1997; 95: 809-13
41. Madan M, Kereiakes DJ, Rund MM, et al. Abciximab readministration for coronary interventions: is it safe? [abstract]. Circulation 1997; 96: I-901
42. Tcheng JE, Kereiakes DJ, George G, et al. Safety of readministration of abciximab; interim results of the reopro readministration registry R^3 [abstract]. J Am Coll Cardiol 1998; 31: 55A
43. Mark DB, Talley JD, Topol EJ, et al. Economic assessment of platelet glycoprotein IIb/IIIa inhibition for prevention of ischemic complications of high-risk coronary angioplasty. Circulation 1996; 94: 629-35
44. Lincoff AM, Mark DB, Califf RM, et al. Economic assessment of platelet glycoprotein IIb/IIIa receptor blockade during coronary intervention in the EPILOG Trial [abstract]. J Am Coll Cardiol 1997; 29: 240A
45. Harrington RA, Lincoff AM, Califf RM, et al. Characteristics and consequences of myocardial infarction after percutaneous coronary intervention: insights from the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT). J Am Coll Cardiol 1995; 25: 1693-9
46. Bowman A, Young S. Graphical comparison of nonparametric curves. Appl Stat 1997; 45: 83-98
47. Strano A, Davi G, Patrono C. *In vivo* platelet activation in diabetes mellitus. Semin Thromb Hemost 1991; 17: 422-5
48. Baim DS, Cutlip DE, Sharma SK, et al. Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). Circulation 1998; 97: 322-31
49. Lefkovits J, Blankenship JC, Anderson KM, et al. Increased risk of non-Q wave myocardial infarction after directional atherectomy is platelet dependent: evidence from the EPIC trial: evaluation of c7E3 for the prevention of ischemic complications. J Am Coll Cardiol 1996; 28: 849-55
50. Ghaffari S, Kereiakes DJ, Kelly T, et al. Platelet GP IIb/IIIa receptor blockade reduces ischemic complications in patients undergoing directional coronary atherectomy [abstract]. Circulation 1996; 94: I-198
51. Bass T, Williams DO, Ho KK, et al. Is an aggressive rotablator strategy preferable to a standard rotoblator strategy in patients with heavily calcified lesions?: a report from the STRATAS trial [abstract]. J Am Coll Cardiol 1998; 31: 378A
52. Williams MS, Coller BS, Vaananen HJ, et al. Activation of platelets in platelet-rich plasma by rotablation is speed dependent and can be inhibited by Abciximab (c7E3 Fab, ReoPro™) [abstract]. J Am Coll Cardiol 1998; 31: 237A
53. Rawitscher D, Levin TN, Cohen I, et al. Rapid reversal of no-reflow using abciximab after coronary device intervention. Cathet Cardiovasc Diagn 1997; 42: 187-90
54. Braden GA, Love WM, Appelgate RJ, et al. Abciximab decreases the incidence and magnitude of non-Q-wave myocardial infarction associated with rotational atherectomy [abstract]. J Am Coll Cardiol 1998; 31: 237A
55. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1997; 96: 1761-9
56. Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia - a serial intravascular ultrasound study. Circulation 1997; 95: 1366-9
57. Vanbelle E, Bauters C, Hubert E, et al. Restenosis rates in diabetic patients - a comparison of coronary stenting and balloon angioplasty in native coronary vessels. Circulation 1997; 96: 1454-60

58. Davi G, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. N Engl J Med 1990; 322: 1769-74
59. Davi G, Gennaro F, Spatola A, et al. Thrombin-antithrombin III complexes in type II diabetes mellitus. J Diabetes Complications 1992; 6: 7-11
60. Kleiman NS, Lincoff AM, Kereiaaakes DJ, et al. Diabetes mellitus, glycoprotein IIb/IIIa blockade and heparin: evidence for a complex interaction in a multicenter trial. Circulation 1998; 97: 1912-20
61. Lefkovits J, Ivanhoe RJ, Califf RM, et al. Effects of platelet glycoprotein IIB/IIIA receptor blockade by a chimeric monoclonal antibody (abciximab) on acute and six-month outcomes after percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1996; 77: 1045-51
62. Khan MM, Ellis SG, Aguirre FV, et al. Does intracoronary thrombus influence the outcome of high risk percutaneous transluminal coronary angioplasty – clinical and angiographic outcomes in a large multicenter trial. J Am Coll Cardiol 1998; 31: 31-6
63. Muhlestein JB, Karagounis LA, Treehan S, et al. 'Rescue' utilization of abciximab for the dissolution of coronary thrombus developing as a complication of coronary angioplasty. J Am Coll Cardiol 1997; 30: 1729-34
64. Steele PM, Chesebro JH, Stanson AW, et al. Balloon angioplasty: natural history of the pathophysiological response to injury in a pig model. Circ Res 1985; 57: 105-12
65. Kereiakes DJ, Broderick TM, Whang DD, et al. Partial reversal of heparin anticoagulation by intravenous protamine in abciximab-treated patients undergoing percutaneous intervention. Am J Cardiol 1997; 80: 633-4
66. The PRISM PLUS Study Group. Inhibition of the platelet glycoprotein IIb IIa receptor tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. New Engl J Med 1998; 338: 1488-97
67. The PRISM PLUS Study Group. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. New Engl J Med 1998; 338: 1498-1505
68. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Eng J Med 1998; 339: 436-43
69. Bauters C, Hubert E, Prat A, et al. Predictors of restenosis after coronary stent implantation. J Am Coll Cardiol 1998; 31: 1291-8
70. Kleiman NS, Mascelli MA, Graziedei N, et al. Ticlopidine potentiates abciximab's ability to inhibit ADP-induced platelet aggregation *in vitro* [abstract]. J Am Coll Cardiol 1997; 29: 241A
71. Kleiman NS, Graziedei N, Lance E, et al. Synergy of abciximab and ticlopidine in patients undergoing intracoronary stenting [abstract]. J Am Coll Cardiol 1998; 31: 238A
72. Kereiakes DJ, Runyon JP, Kleiman NS, et al. Differential dose-response to oral xemilofiban after antecedent intravenous abciximab administration for complex coronary intervention. Circulation 1996; 94: 906-10
73. Kereiakes DJ, Kleiman NS, Ferguson JJ, et al. Pharmacodynamic efficacy, clinical safety and outcomes following prolonged platelet glycoprotein IIb/IIIa receptor blockade with xemilofiban: results of a multicenter placebo controlled randomized trial. Circulation 1998; 98: 1268-78
74. Boehrer JD, Kereiakes DJ, Navetta FI, et al. Effects of profound platelet inhibition with c7E3 before coronary angioplasty on complications of coronary bypass surgery. Am J Cardiol 1994; 74: 1166-70
75. Lincoff AM, Topol EJ, Califf RM, et al. Influence of platelet GP IIb/IIIa receptor inhibition with c7E3 on the sequelae of dissection during percutaneous transluminal coronary intervention [abstract]. J Am Coll Cardiol 1995; 390A
76. Gammie JS, Zenati M, Kormos, et al. Abciximab and excessive bleeding in patients undergoing emergency cardiac operations. Ann Thorac Surg 1998; 65: 465-9
77. Kestin AS, Valeri CR, Khuri SF, et al. The platelet function defect of cardiopulmonary bypass. Blood 1993; 82: 107-17

Correspondence and reprints: Dr *Neal S. Kleiman*, Baylor College of Medicine, The Methodist Hospital, 6565 Fannin Street, MS F1090, Houston, TX 77030, USA.
E-mail: nkleiman@bcm.tmc.edu